# Wolff–Parkinson–White and Preexcitation Syndromes

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## Abbreviations

**AF** Atrial fibrillation
**AP** Accessory pathway
**AV** Atrioventricular
**WPW** Wolff–Parkinson–White syndrome

Preexcitation syndrome is detected in 0.15%–0.5% of the general population. It can be asymptomatic or revealed by a paroxysmal tachycardia and in this case is called Wolff–Parkinson–White syndrome (WPW) with a variable frequency of 4%–90% according to the mode of recruitment. Atrial fibrillation (AF) is rarer. Preexcitation syndrome generally is benign, but ventricular fibrillation may be the first event of this syndrome in 0.1%–0.6% of cases per year. At the time of the curative treatment of preexcitation syndrome by radiofrequency ablation (Warin et al., 1988; Jackman et al., 1991), it is particularly important to detect the forms at risk of sudden death (Klein et al., 1979). Sudden death in preexcitation syndrome is related to the degeneration of AF with high ventricular rates into ventricular fibrillation.

If the prognosis evaluation actually is known, the management of preexcitation syndrome remains dependent on several factors as symptoms, age, sport activity, electrophysiological data, and location of the accessory pathway (AP).

## Mechanism of Preexcitation Syndrome

Ventricular preexcitation syndrome is defined by the premature activation of all or part of the ventricles by atrial activity and is related to the presence of an atrioventricular (AV) AP. APs are present during fetal development and should disappear during the first 3 months of fetal development. The bypass of AV node, a physiologic barrier of AV conduction, explains the possible severity of the disease. Bypass tracts that involve the AV node are relatively rare and do not have the same adverse consequences that can occur with bypass of the AV node. Examples include atrionodal APs (called James or Brechenmacher pathways) and nodoventricular APs (also called Mahaim fibers).

Preexcitation can be associated with a congenital heart disease. The frequency (7.5%–17%) is higher in children and mainly concerns Ebstein's anomaly. All heart diseases have been associated with the preexcitation syndrome with a debatable significance but a higher risk of AF.

## ECG Diagnosis of Preexcitation Syndrome

The surface ECG in sinus rhythm diagnoses preexcitation with a typical pattern associating a short PR interval (<0.12 s in adults) and a widening of QRS complex with a delta wave (Fig. 1). It is often associated with disorders of repolarization. The pattern is

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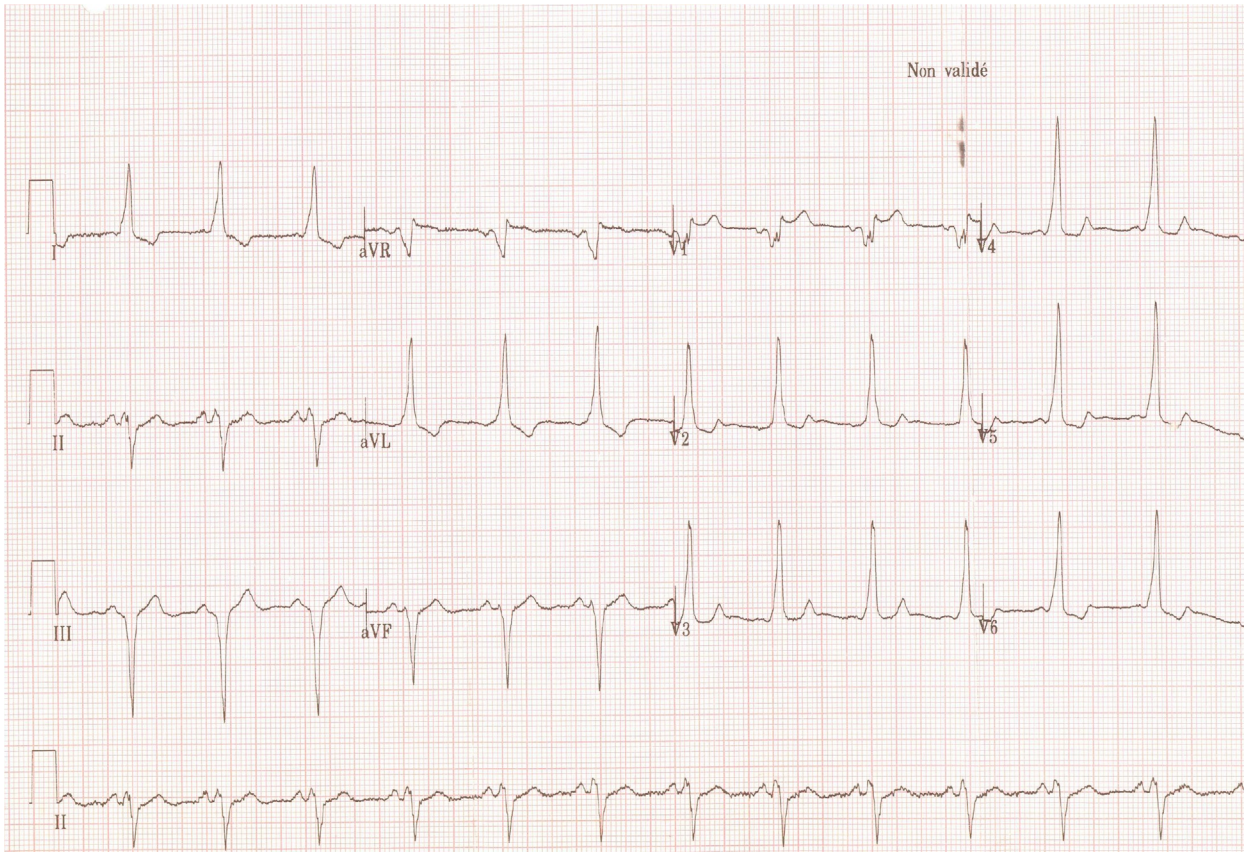


**Fig. 1** Typical pattern of a preexcitation syndrome: short PR interval, large QRS complex, delta wave.

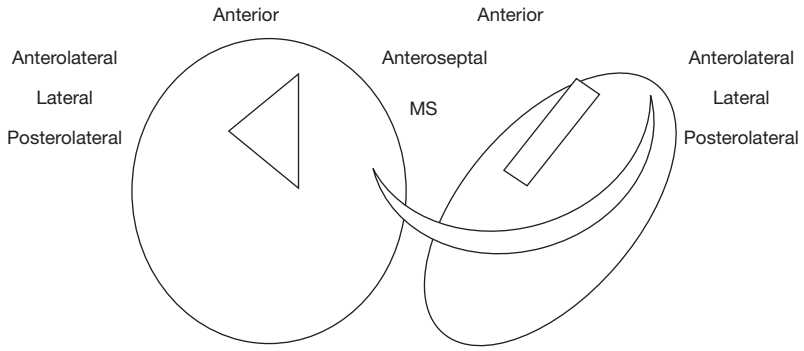


**Fig. 2** Schematic cartoon figure with the different pathway locations.

dependent on the location of AP (different AP locations are shown in Fig. 2) but also of the properties of AV node and His Purkinje system and there is a wide spectrum of types encountered ECG.

The importance of ventricular preexcitation on ECG in sinus rhythm depends on the quality of the nodohisian conduction and the distance between the AP and the normal conduction system (Brembilla-Perrot et al., 2013a). Ventricular preexcitation is less visible the further away that the AP is from the sinus node and the normal AV system. Therefore, classical electrocardiographic criteria of preexcitation are sometimes not visible on ECG recorded in sinus rhythm (Fig. 3).

Spontaneous normalization of ECG with intermittent preexcitation is reported in 20%–30% of cases (Teo et al., 1991; Fujiki et al., 1990). An explanation for the intermittent loss of the delta wave in the preexcitation syndrome may result from precarious conduction over the AP and, as such, would predict a benign prognosis when AF occurs.

Several pharmacological tests were proposed to enhance the pattern of preexcitation when it is doubtful. Under the influence of exercise or emotion, or after isoproterenol infusion, the facilitation of anterograde conduction occurs only in those capable of spontaneous conduction (Easley et al., 1988; Yamamoto et al., 1990; Przybylski et al., 1980). The method was used to differentiate the concealed AP, which has lost its anterograde conduction, from the masked or intermittent preexcitation. Adenosine by blocking

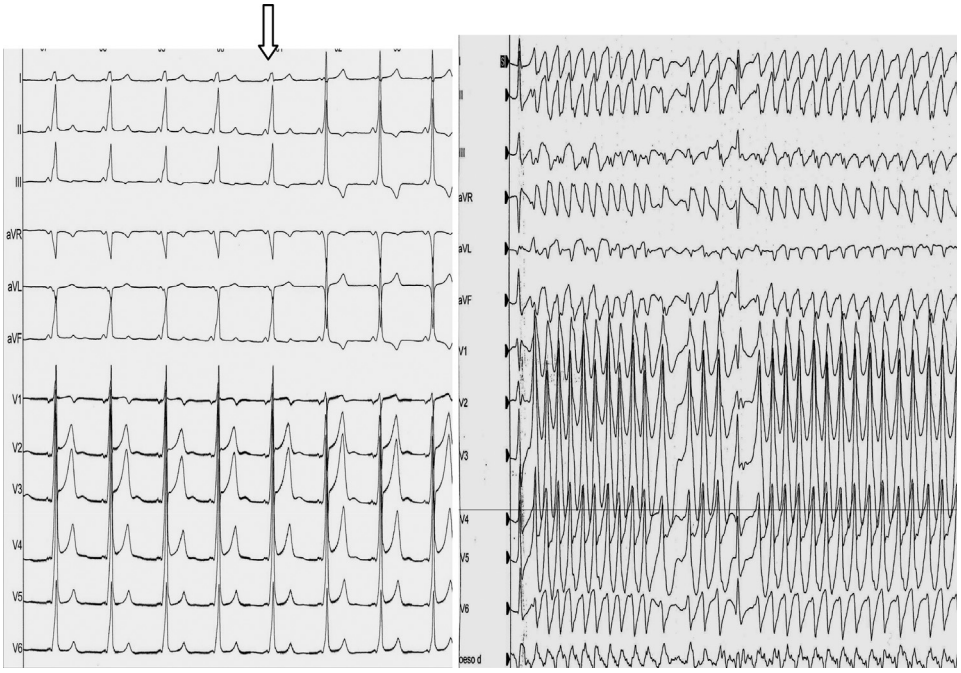


**Fig. 3** Masked preexcitation; the minor signs in sinus rhythm only are visible after ablation of AP (the *arrow* indicates the beginning of ablation). However this patient presented with a spontaneous malignant form (AF with minimal cycle conducted by AP $\leq$250 ms).

the conduction in the AV node was used to unmask preexcitation (Garratt et al., 1990; Morgan-Hughes et al., 1993), but the test rarely is used and it is not specific.

Atrial pacing remains the most reliable technique to identify anterograde conduction over AP.

## Natural History of Preexcitation Syndrome

A pattern of preexcitation is noted among 0.1%–0.5% of the population (Pelliccia et al., 2007). The frequency is higher in young children; AP tends to degenerate earlier than the normal AV conduction system, but the disappearance occurs early generally before the age of 1 year (50%) and more rarely before the age of 12 years (Vignati et al., 2000) and in this last case only when the refractory period of AP is long (Perry and Garson, 1990). Despite a normalization of ECG, the AP still can conduct by the retrograde way explaining the reentrant tachycardia in patients with a normal ECG. When the refractory period of AP noted before the age of 12 years is short, no disappearance can be expected (Chen et al., 1996).

Detected after the age of 5 years, spontaneous regression is rare since the appearance ECG remains unchanged in 75% after a mean follow-up of 7 years (Perry and Garson, 1990). However, electrophysiological data change with an increase in the refractory period of AP but an increased risk of AF (Chen et al., 1996).

## Clinical Signs and Prognosis

The presence of AP exposes to the occurrence of two tachycardias: the most common is the reciprocal tachycardia rhythm called orthodromic AV reentrant tachycardia that usually characterizes the symptomatic forms of the disease (WPW syndrome). This tachycardia uses AV node for the anterograde conduction and AP for the retrograde conduction (**Fig. 4**). Tachycardia presents as a narrow-regular QRS tachycardia. Antidromic tachycardia, related to the anterograde conduction over AP and the retrograde conduction over AV node, is rare and generally a finding of electrophysiological study (**Fig. 5**). The tachycardia presents as a wide QRS tachycardia mimicking a ventricular tachycardia.

The less common is AF (10%) but represents the possible severity of the condition when the AP has a short refractory period: arrhythmia is conducted in 1/1 to the ventricles and can degenerate into ventricular fibrillation, leading to sudden death (**Fig. 6**). The sudden death presentation has mainly been reported in athletes. This is likely because they are subject to a high level of catecholaminergic influence that facilitates the occurrence of arrhythmias and improves conduction in the AP.

However, the prognosis of preexcitation syndrome is discussed according to the type of study population and recruitment. If this is a population detected in preventive medicine, the risk of sudden death is low. However, this event may occur in a subject completely asymptomatic until then, with a similar impact to that of symptomatic subjects: 26%–56% of patients with a

**Fig. 4** Induction of an orthodromic AV reentrant tachycardia, when the refractory period of AP is obtained.

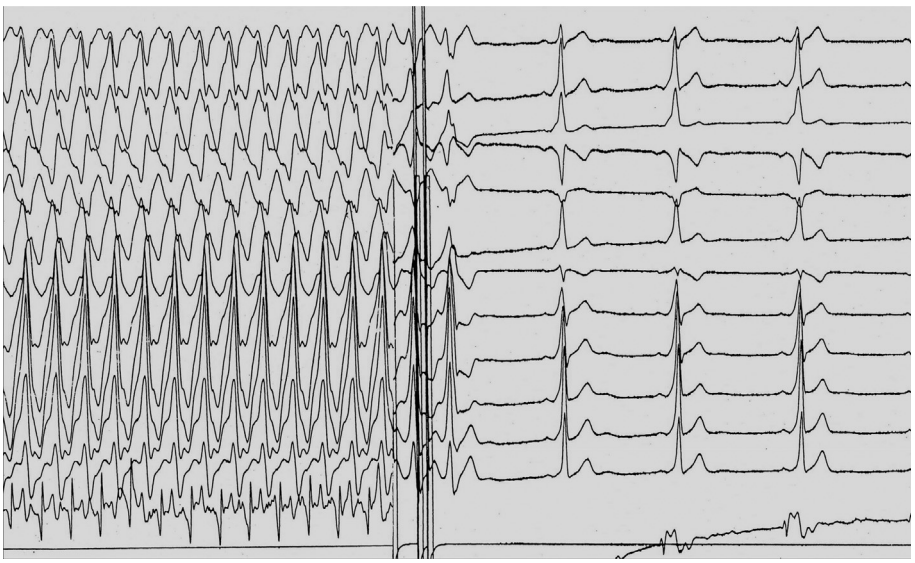

**Fig. 5** Antidromic tachycardia (stopped by atrial stimulation): wide QRS tachycardia presenting as a ventricular tachycardia).

preexcitation syndrome were asymptomatic before sudden death (Klein et al., 1979; Timmermans et al., 1995; Torner Montoya et al., 1991). Sudden death incidence however is low and rare in children (0.02%–0.6% per year) (Timmermans et al., 1995; Munger et al., 1993; Beckman and Lamb, 1968; Fitzsimmons et al., 2001; Pappone et al., 2003; Brembilla-Perrot et al., 2010). The most recent study (Fitzsimmons et al., 2001) reports a sudden cardiac death risk of 0.02%/patient/year, while the supraventricular tachycardia incidence was 1% per patient-year. In addition, adverse events sometimes have been reported in very old patients or very early but exceptionally in young children between 6 days and 12 years, especially in cases of associated congenital heart disease. In symptomatic subjects, adverse event may be due to a prolonged supraventricular tachycardia responsible for ischemic events or heart failure. Sudden death also can be related to the use of drugs that promote conduction in the AP as calcium channel blockers (Brembilla-Perrot et al., 2010) or more rarely digoxin. The risk of sudden death is low, but these sudden deaths are very regrettable, concerning patients with normal heart but the presence of AP and easy to cure. Therefore, the detection of patients with preexcitation syndrome at risk of sudden death is fundamental.

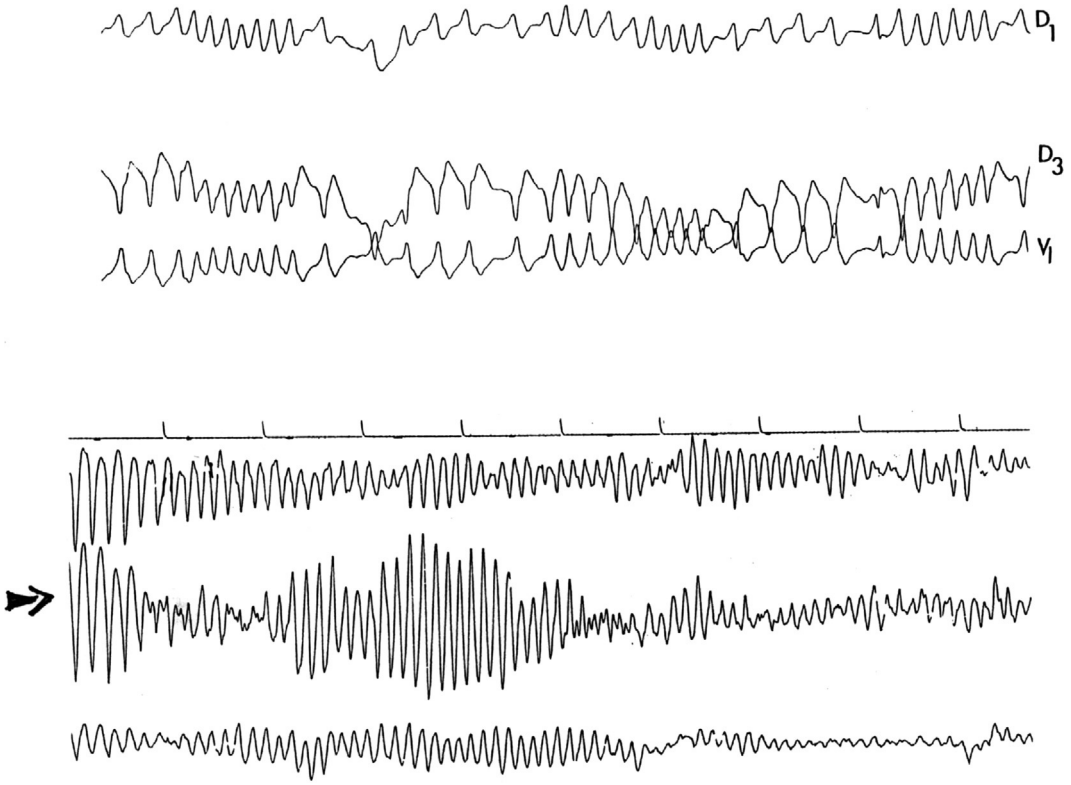


**Fig. 6** AF conducted by AP and degenerating into ventricular fibrillation, classical (but rare cause of sudden death in preexcitation syndrome).

## Methods of Evaluation

Several noninvasive methods have a low sensitivity and specificity:

*ECG*: The pattern of preexcitation on 12 lead surface ECG, the permanent or intermittent feature are not specific enough, although posteroseptal location is more frequently noted in patients at risk of rapid arrhythmias (Wellens, 2005) and the intermittent preexcitation is often associated with a benign form. False tests were reported and other tests are required in subjects at risk of arrhythmias as athletes.

*Exercise testing* was reported at first by Levy et al. (1979) as an important test of prognosis: the abrupt disappearance of preexcitation during an exercise stress testing was proposed as a sign of long refractory period of AP (Levy et al., 1979; Bricker et al., 1985; Strasberg et al., 1980; Sharma et al., 1987; Czosek et al., 2011) (**Fig. 7**) and argues that the AP is benign. In subjects who are not of athletic competition, this disappearance is sufficient to stop the investigations (class I level B grade of recommendation) (Page et al., 2016). While specific, this finding is seldom observed because exercise improves the conduction in the normal AV node conduction system, which can just mask the AP. The gradual loss of preexcitation can be noted in malignant form (Daubert et al., 1986). Therefore, the sensitivity is low (20%) and preexcitation can persist in benign form. Exercise testing is not useful as a provocative test for arrhythmia. However, occasionally the preexcitation will become manifest preexcitation during exercise.

*Holter monitoring* is rarely useful but can detect spontaneous asymptomatic tachycardias in children who rarely complain of tachycardia as in study of Paponne et al. (2004).

*Pharmacological tests* (class I antiarrhythmic drug injection) was used several years ago: the disappearance of the pattern of preexcitation was reported as a sign of long refractory period of the AP (Wellens et al., 1980); however, many false positive tests were reported (Critelli et al., 1984) and the test is no longer used.

Electrophysiological study appears as the most reliable method to establish the prognosis of the preexcitation syndrome.

*Methods*: Patients might be studied by transesophageal (Brembilla-Perrot et al., 2007) or intracardiac route. The first route is indicated in asymptomatic patients and the second in symptomatic patients to perform catheter ablation of AP in a second time. Several advantages concern esophageal route: (1) the patient is not hospitalized and is leaving hospital after study. Only those with induced atrial arrhythmias are awaiting and followed until sinus rhythm is restored. (2) No radiation is used (Bacher et al., 2005) and catheter-related risks are avoided (Paponne et al., 2004; Vitello et al., 1998). (3) The method is feasible from the age of 5 years without sedation (and in newborns) while general anesthesia is required in young children for an intracardiac catheter study. (4)

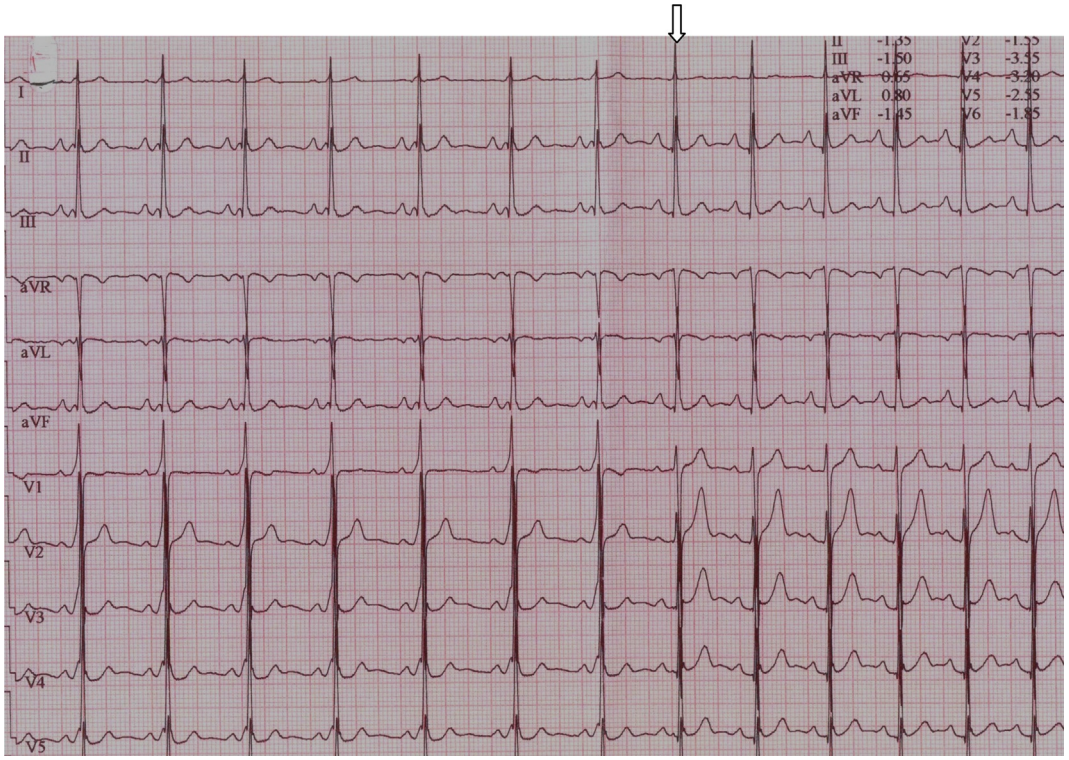


**Fig. 7** Abrupt disappearance of preexcitation, sign of a benign form.

There is an overestimation of AF induction in the young patients when intracardiac study is used (Brembilla-Perrot et al., 2001). However, there also some disadvantages. (1) The main problem is related to the appropriate placement of the esophageal electrode complicated by an important gag reflex in children younger than 10 years. (2) The method is associated with chest pain and anxiety related to pacing; the presence of the parents recommended in young children and rapid rates of pacing should be avoided in children. (3) Finally, it is not possible to pace atria in 5%–10% of patients.

It should be noted that all electrophysiological studies in preexcitation syndromes may be dangerous and should be performed with an external defibrillator ready to be used, because a poorly tolerated arrhythmia can be induced in asymptomatic or symptomatic patients.

Cardiac stimulation is performed with a biphasic stimulator. Pulses of 1 ms duration and 0.5–3 mA are used for intracardiac study and pulses of 10 ms duration, output from 8 to 18 mA are used for esophageal study. For a simple intracardiac electrophysiological study, only one catheter is needed: a bipolar silicone esophageal lead or one bipolar intracardiac catheter.

The classical protocol is as following:

Incremental atrial pacing is performed until second degree AV block occurred. The maximal rate of 1:1 conduction over AP is noted.

Programmed atrial stimulation at a basic cycle length of 600 and 400 ms with the introduction of one and two extrastimuli is performed: the disappearance of preexcitation syndrome indicates that the refractory period of AP is longer than that of the AV node. The coupling interval (S1S2 or S2S3) at which the AP becomes refractory will depend on the drive train cycle length (S1S1 interval), with shorter drive trains associated with shorter refractory periods.

The method also is used to induce a supraventricular tachycardia, generally an orthodromic tachycardia, rarely an antidromic tachycardia, or an atrial tachycardia or fibrillation.

These data should be studied under adrenergic situations, except in patients who have a form at risk of sudden death in control state. Two methods are used: atrial pacing might be repeated during an exercise testing which is the most physiological situation, but which is difficult to perform. Many authors prefer the infusion of isoproterenol, a beta-adrenergic drug and which is simpler to use during an electrophysiological study (Crick et al., 1985; Mabo et al., 1992). Isoproterenol (0.02–1 μg $min^{-1}$) is infused to increase the sinus rate to >130 $min^{-1}$ and the pacing protocol is repeated (Wellens et al., 1981). Beta-adrenergic stimulation results in shortening of the anterograde AP refractory period and in increasing in ventricular rates during atrial pacing and during AF. Isoproterenol test was also previously used to verify the efficacy of antiarrhythmic drug before the time of catheter ablation of AP. The loss of efficacy of some antiarrhythmic drugs was demonstrated after isoproterenol administration (Brembilla-Perrot et al., 1985), although the use of isoproterenol infusions in this setting can be controversial.

At the end of the protocol, using the following definitions, the prognosis of the preexcitation syndrome can be established:

- Sustained AF or reciprocating tachycardia is defined as a tachycardia that is longer than 1 min. The exact duration of induced tachycardia to be considered as pathological is controversial and varies from 30 s up to 5 min.
- Conduction over the AP evaluated by the measurement of the shortest atrial cycle length at which there is 1 to 1 conduction over the AP and the shortest atrial tachycardia cycle length at which there is 1 to 1 conduction over the AP.

The preexcitation syndrome is considered as presenting a risk of sudden death when the following association is observed (Brembilla-Perrot et al., 2010; Milstein et al., 1986; Klein et al., 1989): sustained AF is induced and the shortest RR interval between preexcited beats is ≤250 ms in the control state in adults, ≤220 ms in children (Bricker et al., 1985) or ≤200 ms during isoproterenol infusion (Strasberg et al., 1980; Brembilla-Perrot et al., 2007, 2014). These criteria were those classically retained before the recommendations of 2012 (Cohen et al., 2012). It should be noted that for Klein et al. (1979) have broken up the risk of sudden death on the basis of the shortest RR interval during AF as follows: (1) definite risk, shortest preexcited RR interval <220 ms; (2) probable risk, shortest preexcited RR interval <250 but >220 ms; (3) possible risk, shortest preexcited RR interval <300 but >250 ms; and (4) negligible risk, shortest preexcited RR interval >300 ms. Electrophysiological study now was considered as negative if no tachycardia was induced and a long refractory period of AP (>250 ms in control state and >200 ms after isoproterenol) was noted. Recent papers have looked at labeling a patient as being considered high-risk (malignant) only using minimal cycle length of preexcitation in the absence of inducible AF: in the PACES/HRS 2012 Management of Asymptomatic Preexcitation Recommendations it was recommended that in the absence of inducible AF the minimal cycle length of preexcitation should be used as an alternative (Cohen et al., 2012).

### General Results of Electrophysiological Studies

The exact nature of the preexcitation syndrome is assessed. Most preexcitations are related to an AV AP (Kent bundle): the degree of preexcitation increases during premature atrial stimulation until the refractory period of AP is reached, because the conduction does not change in AP with the shortening of atrial cycle length and increases in the AV node. Rarely preexcitation is related to a nodoventricular AP or Mahaim bundle; the degree of preexcitation remains unchanged during premature atrial stimulation. Furthermore, atrial pacing also is an important method to detect or confirm or infirm the presence of a preexcitation syndrome when delta wave is not evident.

In symptomatic patients it is easy to reproduce the spontaneous tachycardia. Reentrant tachycardias are easily induced by stimulation (**Fig. 3**): orthodromic tachycardia which is a reciprocating tachycardia using the normal AV conduction system for the anterograde conduction and the AP for the retrograde conduction is rarely induced in asymptomatic patients (<10%) (Critelli et al., 1984; Brembilla-Perrot et al., 2007) but represents the most frequent tachycardia of symptomatic patients complaining of tachycardia and palpitations (90%) (Rinne et al., 1987).

In patients with spontaneous adverse events the sensitivity of electrophysiologic study to induce sustained AF with the shortest RR interval between preexcited beats ≤250 ms in the control state or ≤200 ms after isoproterenol infusion also is excellent (Brembilla-Perrot et al., 2010). Therefore, electrophysiological study is considered as the most sensitive and specific method to assess the prognosis of preexcitation (Wellens, 2005; Milstein et al., 1986; Klein et al., 1989).

AF easily is induced during intracardiac studies by salvos of rapid atrial stimulation and is not specific (Brembilla-Perrot et al., 2001). AF induction by intracardiac programmed stimulation is obtained in 27%–75% according to the studies, in asymptomatic patients and in patients with only documented reentrant tachycardia (Rinne et al., 1987); AF is induced in 95% of those with documented AF (Rinne et al., 1987). The important variations of the incidence of induced AF depends on the technique of programmed stimulation, on the interpretation of the duration of induced arrhythmia and on the use of isoproterenol infusion or other means to reproduce the effects of adrenergic stimulation. In our experience, the induction of AF during transesophageal pacing is more clinically significant than with intracardiac pacing (Brembilla-Perrot et al., 2001): AF induction is rarer with TEE pacing from 10% to 30% according to the age in patients without documented AF (less false positives) and remained sensitive to induce AF in those with documented AF (95%). The incidence of induced AF also depends on the presence of associated heart disease and on the age of the patient: AF is rarely induced in children younger than 10 years (Brembilla-Perrot et al., 2007), is induced in 20% of teenagers and adults without heart disease and becomes relatively frequent in elderly (31%) (Brembilla-Perrot et al., 2016).

Ventricular tachyarrhythmias also are easily used in asymptomatic or symptomatic patients by programmed ventricular stimulation and are not specific in preexcitation syndrome: ventricular fibrillation is induced in 4% syndrome and nonsustained multiform ventricular tachycardia in 37% of them (Brembilla-Perrot et al., 1987).

Antidromic tachycardia which is a reciprocating tachycardia using the AP for the anterograde conduction and the normal AV conduction system is a rare finding (5%), more frequently noted in young patients with a good retrograde normal VA conduction or in patients with several APs and seems more frequent in patients at risk of rapid arrhythmias.

- The presence of syncope does not increase the risk to find a potential dangerous form in adults (Auricchio et al., 1991); in young patients (<25 years) the significance of syncope seems different and associated with occurrence of AF with a rapid ventricular response (Paul et al., 1990; Brembilla-Perrot et al., 2013b). Reentrant tachycardia remains the main cause of syncope (Brembilla-Perrot et al., 2013b).

- The incidence of forms considered at risk of rapid arrhythmias is similar in symptomatic and asymptomatic patients and concerns 10% of the total population with preexcitation (Milstein et al., 1986; Auricchio et al., 1991; Brembilla-Perrot and Ghawi, 1993; Michelucci et al., 1988; Fan et al., 1991), independently on the age of the patient (Auricchio et al., 1991).
- In asymptomatic patients important variations of results also are reported. The percentage of induction of reentrant tachycardias varies from 11% to 50%. The percentage of AF induction varies from 0% in children <11 years (Brembilla-Perrot et al., 2007) to 20%–50% in adults. The percentage of induction of AF induction with a short RR interval between preexcited beats varies from 15% to 25%. These variations depend on the age of patient (Michelucci et al., 1988; Fan et al., 1991). Children considered as asymptomatic sometimes have spontaneous tachycardia without a clear feeling. In our experience, AVRT induction is not rare (most children recognize the tachycardia usually well tolerated). In the study of Paponne et al. (2004) five apparently asymptomatic patients in the control group had documented silent episodes of sustained AF at Holter monitoring. They remained asymptomatic despite extremely rapid ventricular responses over AP. High incidences of events (one sudden death and two ventricular fibrillations) were reported in these "asymptomatic" children, who had documented rapid AF and were not treated.

The exact clinical significance of the electrophysiological form at risk of sudden death in asymptomatic patients remained controversial. A low incidence of adverse events during a mean follow-up of 4 years was reported in previous studies using the intracardiac evaluation of preexcitation (Klein et al., 1989; Brembilla-Perrot and Ghawi, 1993; Leitch et al., 1990). However several studies of Pappone and Santinelli recently have shown that electrophysiological study could predict sudden death of asymptomatic patients (Pappone et al., 2003; Paponne et al., 2004; Santinelli et al., 2009). In 2009 (Santinelli et al., 2009) they consider that a short AP ERP <240 ms, the tachycardia inducibility and the presence of multiple APs are the main factors of risk in children.

Besides the serious forms, 75%–80% of asymptomatic patients have a benign form of preexcitation.

### Indications of Electrophysiological Studies in Preexcitation Syndrome

The indications are now large in symptomatic patients to perform in a second time the catheter ablation of patients complaining frequent sustained tachycardias. The study should be performed using intracardiac catheterization (Page et al., 2016).

In patients with syncope, but no documented tachycardia, electrophysiological study is necessary and might be performed by transesophageal route because the role of the AP in the occurrence of syncope remains rare in adults (Auricchio et al., 1991).

In patients who have a documented rapid or syncopal AF, electrophysiological study is not indicated, because direct AP catheter ablation is recommended (Page et al., 2016). The induction of AF should be avoided.

In asymptomatic patients, the indications are more debatable (Page et al., 2016).

- In asymptomatic patients who are not competitive athletes, the abrupt disappearance of preexcitation is sufficient to stop the investigations (class I, level B grade of recommendation) (Czosek et al., 2011; Page et al., 2016).
- In other patients it is recommended to use techniques with a low risk of adverse events but a good diagnostic value is mandatory. Esophageal route when possible should be the preferred means of evaluation, because the probability to find a form at potential risk of sudden death remains rare (10%).

Some indications of a systematic electrophysiological are actually recommended:

1. Most of sudden deaths have the peculiarity to occur during exercise (Wiedermann et al., 1987). Because of the important development of sports from the infancy to the elderly, it is important to detect those patients with a preexcitation at risk of sudden death who practice a sportive activity; the indication generally begins after 10 years, because the risk of induction of a rapid AF is very small and the level of sport still low. The competitive athlete should be studied in all ranges of age (Cohen et al., 2012; Heidbüchel et al., 2006). The indications are also recommended in professions with a high level of sportive activity (policemen, soldier, fireman, . . .).
2. Electrophysiological study is recommended in patients with high responsibility profession such as professional pilot (plane, truck, bus, train).
3. These indications are largely accepted in teenagers and adults up to middle age. The indications in children or elderly are more controversial.

In children, it is rare to indicate an electrophysiological study <10 years of age because AF is unusual in the absence of associated heart disease (Vignati et al., 2000; Brembilla-Perrot et al., 2007). The recommendations of 2005 (Wiedermann et al., 1987) reported that "in children <12 years of age, the risk of AF and/or SCD is considered virtual, and assessment of the risk may be postponed." However the age of 5 years is the recommended age for Pappone (Pappone et al., 2003; Santinelli et al., 2009). Furthermore, conduction over AP and normal AV conduction system are more rapid without probably a clinical significance: in the study of Bromberg (Bromberg et al., 1996; Sarubbi et al., 2005) a cycle length <220 ms in basal state is considered at risk of severe arrhythmias in children <18 years; in adults, the value of ≤250 ms is admitted as a sign of a dangerous form. However, because rare sudden deaths were reported in children (Santinelli et al., 2009; Sarubbi et al., 2005), the indications should be large in young children practicing sports competition and in all children >10 years.

In elderly, the shortest atrial pacing cycle length with 1:1 anterograde conduction via the AP increased progressively with age (Brembilla-Perrot et al., 2016; Michelucci et al., 1988; Fan et al., 1991; Rosenfeld et al., 1991). However, the propensity for AF was shown to be higher in older patients compared to younger patients (Brembilla-Perrot et al., 2016; Michelucci et al., 1984). While the exact mechanism is uncertain, degenerative changes associated is the most commonly proposed mechanism and the dispersion of

atrial refractoriness increases progressively with age (Michelucci et al., 1984). The risk to have a severe arrhythmia as the first manifestation of preexcitation syndrome in an old patient was previously reported (Brembilla-Perrot et al., 2003, 2010). High-level sporting activity is rare in elderly, but other causes for adrenergic tone increase might be encountered, as important surgery.

Therefore, because of the increase of the sport in all ranges of age and in particularly in young children or after 60 years, the risk of occurrence of a potentially severe arrhythmia in an asymptomatic patient should be not underestimated.

## Management of Preexcitation Syndrome

### Acute Treatment of Arrhythmias (Page et al., 2016)

In the case of hemodynamically stable narrow-complex QRS tachycardia, after failure of sinocarotid massage, adenosine triphosphate injection is the recommended treatment (class I, level B). Rarely other treatments are required (class IIA): Intravenous diltiazem, verapamil (level of evidence: B-R), or beta blockers (level of evidence C-LD) can be effective for acute treatment in patients with orthodromic AV reentrant tachycardia who do not have preexcitation on their resting ECG during sinus rhythm. Intravenous amiodarone preferentially is used in Europa after failure of other drugs.

In the case of antidromic tachycardia or AF conducted by the AP, the treatment depends on tolerance. In poorly tolerated tachycardias, urgent cardioversion after sedation is the recommended treatment (class I, level B).

In other cases calcium inhibitors and digoxin are prohibited because they facilitate the conduction over AP and are the causes of ventricular fibrillation (Brembilla-Perrot et al., 2010).

Amiodarone or preferentially intravenous flecainide (1 mg $kg^{-1}$) when associated heart disease is excluded are the recommended treatments.

### Preventive Treatment (Page et al., 2016)

Ablation of AP, which is a curative treatment, now is recommended in preexcitation syndrome requiring a treatment. However, the results and risks of the method still need to be compared with the symptoms and preexcitation-related risks. Age of the patient, competitive sport activity, particular jobs (fireman, military, train, or airplane pilot), and location of AP are some of several factors that should be considered before the indications of treatment.

#### *Risks and benefits related to the ablation of the AP*

Introduced in 1990, the ablation of AP is able to permanently cure the subject with a ventricular preexcitation syndrome (Warin et al., 1988; Jackman et al., 1991). The immediate success of ablation has increased since 1990 and is currently around 93/95%. Nevertheless, it is lower in case of right lateral location (78%), in very young children, and in the presence of heart disease, particularly in cases of Ebstein's anomaly.

Also it is necessary to consider the risk of recurrence of preexcitation, which averages 10% and is dependent on the location of AP (right sided 24%, midseptal 17%, left AP 5%). The phenomenon usually occurs early (first 2 months). In addition, the risks of complications also have decreased from 4.3% to 2.9% (average 3%). It remains most common in young children: Mortality fortunately is exceptional (0%–0.2%). The complications are mainly related to radiation exposure (Bacher et al., 2005) (less important if using a mapping system is used), vascular access (e.g., hematoma, pneumothorax, arteriovenous fistula), catheter manipulation (coronary dissection, perforation of the coronary sinus, microemboli), and the application of radio frequency (risk of complete AV block, coronary stenosis) (Vitello et al., 1998; Fujiki et al., 1990; Schuffer et al., 1996). Complete AV block is a known complication of the ablation of a parahisian AP and has been reported for posteroseptal AP. The risk is exceptional when using cryoablation in place of radiofrequency ablation, but this technique is not used in all the teams because of a risk of higher recurrence of preexcitation.

#### *Indications of ablation in 2016 (Page et al., 2016) (Table 1)*

The recommendations are based on the 2012 publications in children (Cohen et al., 2012), on the 2015/2016 data in the symptomatic or asymptomatic adults (Page et al., 2016). Several elements are to be considered:

A. The patient is symptomatic or not;
B. What is the patient's age?
C. Does the patient participate in a competitive sport or is does their profession prohibit the presence of an AP (e.g., pilot)?
D. What is the location of AP?

*A—The subject is symptomatic (reentrant tachycardia or AF with rapid conduction over the AP)*: Ablation is recommended (class I level B), especially in adults. Drug treatment is a class I level C recommendation only when AP is concealed (Page et al., 2016).

It must be remembered that successful ablation prevents the risk of AF than in subjects <50 years (Dagres et al., 2001) and especially when it was proved that AF was due to reciprocal tachycardia rhythm. Otherwise ablation is used to prevent too rapid conduction through the AP during AF. This fact has been confirmed by Bunch et al. (2015) who also showed a lower mortality in patients who underwent ablation.

**Table 1** Indications of ablation of AP

| *Class* | *Level of proof* | *Indications* |
|---|---|---|
| I | B | • Symptoms (tachycardia)<br>• No symptoms: malignant form at electrophysiology<br>• No symptoms: sport competition, job at risk |
| II a | B | Asymptomatic: malignant form at electrophysiology<br>Symptomatic; child |
| III | | Asymptomatic, benign form at electrophysiology |

Malignant form at electrophysiology (AF induced with minimal cycle conducted by AP $\leq$250 ms).
Benign form: no inducible tachycardia, refractory period of the AP >250 ms.

*B—The subject is asymptomatic*: Ablation is recommended (class IIa level B) in the case of detection of a form to high risk at electrophysiology study (AF with a minimum cycle length conducted by AP $\leq$250 ms) but also systematically in the subject exercising a profession at risk (e.g., pilots or drivers) (Page et al., 2016).

It should be noted that the simple monitoring of asymptomatic individuals also has the same class of recommendation (class IIa level B) and a recent study of Papponne and Santinelli (Pappone et al., 2014) the prognosis of preexcitation syndrome essentially depends on intrinsic electrophysiological properties of AP rather than on symptoms. For these authors ablation performed during the same procedure after electrophysiological testing is of benefit in improving the long-term outcomes.

*C*—In young children, the indications are discussed because of radiation risks and catheterization complications (Bacher et al., 2005; Vitello et al., 1998). They should be discussed with parents (Cohen et al., 2012).

AF risk is low unless associated with congenital heart disease. In addition, the involution of AP is possible before the age of 12 years if the AP refractory period is long and finally the sports in competition do not apply to young children. Drug treatment is usually effective in young symptomatic children.

In practice, the ablation can be exceptionally indicated before the age of 12 if antiarrhythmic drugs or beta-blockers are ineffective or not tolerated but requires general anesthesia.

In 2012, ablation is recommended (class II level A) in asymptomatic children ($\geq$8 years) if AF with rapid conduction is induced and if reciprocal tachycardia is inducible (class II, level B) (Cohen et al., 2012). However the recommendation is the same (class II level B) in the absence of inducible tachycardia in special cases (sports) and in the absence of parahisian location. The absence of induction of tachycardia and the induction of AF with a driving cycle >250 ms leads to a simple monitoring (recommendation of class II (level A).

*D—Athletic competition*: Evaluation and ablation indications are wider. Sport is authorized without ablation if the subject is asymptomatic and if systematic electrophysiological study shows that this is a benign form (refractory period >250 ms and no inducible tachycardia) (Heidbüchel et al., 2006).

*E—Location of AP*: In the case of parahisian location, the risk of complete AV block is important except when cryoablation is used, but there is a high risk of recurrence (Swissa et al., 2015). This location is particularly important to consider in asymptomatic subjects where ablation indications remain questionable.

In conclusion, several data should be considered in patients with a preexcitation syndrome

- Confirmation of the diagnosis.
- Evaluation of the prognosis. Electrophysiological study is the best means to define this prognosis. The method is easily performed in the out-patient clinic by transesophageal route. The indications should be large to avoid the misdiagnosis of a form at risk of rapid arrhythmias. This dangerous form is relatively rare in asymptomatic patients, symptomatic patients, or those with unexplained syncope. Most of these patients (>85%) would be allowed to continue their activities, without specific treatment, because they have a benign form of preexcitation syndrome.
- Discussion of the treatment. Ablation of AP is required in symptomatic subject. It remains controversial in asymptomatic subject except in the case of sport competition or in the case of a profession at risk and in the in case of detection of a potentially serious form at electrophysiology (induction of AF conducted by the AP with a $\leq$250 ms cycle length). The recommendations are contradictory because the risks are low and ablation does not have a success rate of 100%. The indications rarely are needed in children before 12 years.

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